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## Enhancing adherence in patients with COPD

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# CHAPTER 10

## GENERAL DISCUSSION

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**Partly based on:**

Van Boven JF, Trappenburg JC, van der Molen T, Chavannes NH.  
Towards tailored and targeted adherence assessment to optimize asthma management.  
*NPJ Primary Care Respiratory Medicine* 2015; 25: 15046

## GENERAL DISCUSSION

The objective of this thesis was to identify targets for interventions to optimize medication adherence in COPD and to study the economic implications of such interventions that enhance medication adherence.

### Main findings

In chapter 2, a systematic review was performed with the aim to summarize the available evidence on the clinical and economic impact of non-adherence in patients with COPD. Results from 12 studies showed that outcomes associated with non-adherence included increased hospitalizations and emergency department visits, increased mortality, increased total healthcare costs, decreased quality of life and decreased productivity. Therefore, non-adherent patients with COPD were highlighted as a target for potentially highly cost-effective interventions.

In chapter 3, the economic impact of COPD in the working age population was assessed. While direct healthcare costs such as medication, GP visits and hospitalizations are well described in literature, less was known regarding the impact of COPD on societal costs like productivity, disability pensions and tax revenue losses. It appeared that these costs were considerable and even exceeded direct medical costs. Thus, potential gains from interventions in this population are large.

In chapter 4, a factor that may be related to non-adherence in COPD, the occurrence of oropharyngeal side effects, was described. Notably, candidiasis presents a problem in this respect. Using a prescription sequence symmetry analysis, the highest prevalence of oral candidiasis was found in the first three months after initiation of inhaled corticosteroids. After one year, the prevalence of oral candidiasis was lower but still elevated, stressing the need for reinforcement of inhalation instructions.

Subsequently, in chapter 5, the impact of reimbursement on treatment adherence to smoking cessation medication was studied. It was found that not only the likelihood of initiating pharmacological smoking cessation treatments, but also the extent of adherence to these treatments seems higher during periods of reimbursement. The effect was more profound in varenicline as compared to bupropion.

Chapter 6 focused on the impact of inhaler device on patients' persistence with long-acting beta-agonists. There was no impact of inhaler device (multiple-dose versus single-dose inhalers) on COPD patients' persistence with long-acting beta agonists. Notably, over 80% of patients that initially seemed to discontinue long-acting beta agonists, re-started their initial medication or switched inhalers or medication within one year.

In chapter 7, a model was developed to predict mean utility values from data derived from the Clinical COPD Questionnaire (CCQ). This model, or mapping tool, was needed as only few clinical studies did include an outcome measure of general health-related quality of life. On a group level, the mapping model predicted mean EQ-5D values that were similar to the

observed mean values. However, on an individual level, the mapping models overestimated the values of people with low observed EQ-5D values and underestimated the values of people with high observed values. Mapping the CCQ onto the EQ-5D is therefore not recommended and should only be used when no other options are available. Preferably, future clinical COPD studies should include the EQ-5D in their list of outcomes.

Chapter 8 described the economic evaluation of a randomized controlled trial performed in over 50 community pharmacies in Belgium (PHARMACOP). The program focused on improving inhalation technique and medication adherence in patients with COPD. In the cost-effectiveness study of the PHARMACOP-trial, it was demonstrated that improving inhaler adherence in community pharmacies is a cost-saving strategy compared with usual care. Improving inhaler adherence should be considered before adding new therapies. Moreover, large scale implementation and reimbursement of these types of protocolled interventions is recommended.

Chapter 9 described the evaluation of the MeMO-COPD program, performed in 20 community pharmacies in The Netherlands. This intervention program aimed to target, using a multidisciplinary approach, symptomatic COPD patients at high risk with suboptimal pharmacotherapy. The MeMO-COPD program appeared an efficient and cost-effective method to target high-risk patients with COPD. Continuous detection of suboptimal pharmacotherapy and risk factors by the pharmacist, followed by multidisciplinary interventions by pharmacist, GP, physiotherapist and dietician offers potential for targeted and tailored or personalized healthcare as opposed to current widespread 'one-size-fits-all' interventions.

**Interpretation**

The work described in this thesis offers a wide range of targets and interventions to be focused on, when optimizing pharmacotherapy in patients with COPD. Notably, optimizing pharmacotherapy in patients with COPD may have more effects than just an increased effectiveness of COPD medication. COPD patients are usually suffering from multi-morbid conditions, that is, comorbidities and polypharmacy are common. Optimizing pharmacotherapy to COPD medication may result in better adherence and self-management related to other diseases (such as cardiovascular disease or osteoporosis) as well. Moreover, when healthcare providers would achieve sustained changes in patients' behavior, long-lasting effects on for example hospitalizations may be seen.

In COPD patients, good adherence to medication has been linked to decreased mortality and hospitalization rates. Interestingly, in previous studies, effects were not only seen in patients that are adherent to medication, but in patients adherent to placebo as well.<sup>1</sup> This phenomenon has been described as the 'healthy adherer effect'.<sup>1,2</sup> It implicates that patients adherent to their medication, have an overall more healthy lifestyle; they may be more adherent to other treatment regimens, be more physically active, attempt to quit smoking and stay on a healthy diet. In other words, medication non-adherence may be an indicator of patients' shortage of disease- and self-management skills. This reveals an important opportunity for the healthcare

provider in actively searching for non-adherent COPD patients and target your interventions to these patients. Using this strategy, not only healthcare providers' time is more efficiently spend, but also the cost-effectiveness of disease management interventions is expected to increase as non-adherence is markedly associated with worsened economic outcomes.<sup>3</sup>

*Adherence-enhancing interventions in their context*

Regarding COPD treatment, one should realize that the studies in this thesis do by far not cover the total treatment of COPD. During the process from diagnosis, prescription, dispensing and using COPD medication, a wealth of potential improvements have been identified in the past decades.

The roadmap presented in figure 1 presents an overview of several aspects that can be optimized in order to reach optimal COPD outcomes, maximizing quality of life primarily through preventing exacerbations.

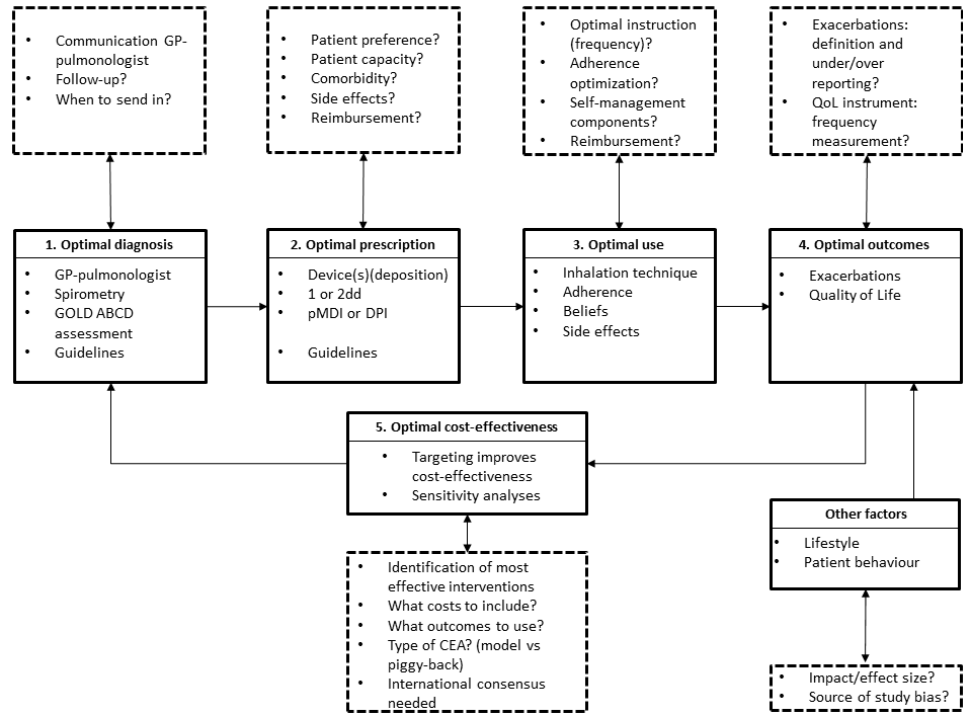


Figure 1: The road towards optimal COPD outcomes: dashed lines indicate room for future research

## Recommendations for future research

The major topics this thesis focused on were related to the cost-effectiveness of adherence enhancing interventions (Figure 1, box 5). Also, some work was specifically related to adherence itself. Especially, the measurement of adherence and the definition of adherence remain major issues on which consensus is required.

### *Adherence taxonomy*

The most recent review conducted that focused on adherence taxonomy in general (not respiratory specific) was by *Vrijens et al.*<sup>4</sup> They performed a systematic medical literature search (using literature up to 2009) and distinguished three phases of adherence: 'Initiation', 'Implementation' and 'Discontinuation'. These phases are a useful start, but there is still much open to interpretation, especially as there was no section addressing inhaled respiratory adherence. In particular, this should be further specified as in this area of chronic diseases, not only the issues of medication intake intensity and persistence play a role, but also the quality of administration (i.e. inhalation technique).<sup>5,6</sup> There may be patients that inhale twice day, in accordance with the recommendation of their healthcare provider, however if the quality of their inhalation falls short, no medication will reach the lungs.

It is considered a major priority to stimulate future work to be produced in this area, including standardization of taxonomy. Ongoing variation in the taxonomy used to define adherence will lead to results that are difficult to compare across studies.<sup>7</sup> Ultimately, this will limit research efficiency as well as obtaining usable insights available for enhancing patient benefits.<sup>8</sup>

Therefore, there is a clear need to reach consensus on the taxonomy used, especially in the area of respiratory medicine.

### *Adherence measurement*

A further potential large gain is expected from improvements of methods to measure adherence. While guidelines to assess the cost-effectiveness of interventions are generally well established, the methods to assess adherence, especially in the respiratory area, are less well developed. From this thesis it became clear that targeting non-adherent COPD patients for specific interventions resulted in favorable cost-effectiveness. In COPD, besides medication intake intensity and persistence, the quality of administration, that is, inhalation technique is essential. Especially the latter is still hard to measure routinely. Therefore, the need for more research regarding innovative adherence measurement methods is emphasized. Future developments in the field of inhalers appear promising. Ideally, new inhalers will enable us to provide both a qualitative measurement of adherence (e.g. inhaler handling and inhalation technique) and continuous quantitative measurements. The quantitative measures include frequency of, exact timings of, and time-interval between inhalations. Electronic monitoring devices, attached to or integrated in inhalation devices, appear the most promising to capture both aspects.<sup>9</sup> These electronic devices have been recommended as the reference standard to assess medication adherence

in both research as well as clinical settings.<sup>10</sup> Technically, these technologies have shown their feasibility and even some have already been on the healthcare market for almost 20 years, although they are primarily used in small-scale research settings.<sup>11</sup> Examples of monitoring devices that are able to log the date and exact timings are the SmartMist, Doser CT, MDIlog and the Nebulizer Chronolog, with studies demonstrating sufficient accuracy for all these devices.<sup>12,13</sup> A more recent development is the Propeller Health sensor that not only keeps a record of time and date, but also of location of use.<sup>14</sup> Another development is the Smartinhaler that automatically sends usage data to a mobile application or computer via Bluetooth and it can provide discrete audio-visual reminders if the patient forgets to take the prescribed medication.<sup>15</sup> Yet, both devices still do not assess the quality of inhalation. A promising new technique relies on the use of acoustic inhalation measurements. In research settings, time stamped acoustic recordings seemed to be a suitable method for monitoring inhalation technique over time.<sup>11,16</sup> Interestingly, an association between better adherence and changes in quality of life and peak expiratory flow was only found, when adherence was operationalized as both time of use and inhalation technique, and not for time of use only.<sup>11</sup> These developments illustrate that some of the technologies using electronic monitoring components in asthma and COPD management are already introduced and available, whereas more large-scale and real-life applications still lack. Notably, more research is required to underpin such further spread of these technologies.

## Recommendations for clinical practice

### *Multidisciplinary collaborations*

For all primary care healthcare providers involved in the treatment of patients with COPD, it is highly recommended to further establish inter professional collaborations on a local level (Figure 2).

In previous studies, multidisciplinary interventions have already shown their value in the treatment of COPD patients.<sup>17</sup> The last chapter of this thesis confirmed the effectiveness and cost-effectiveness of close collaborations in primary care. GPs, pharmacists, physiotherapists and dieticians have all been playing their individual roles in the primary care treatment of COPD, but often intensive collaboration with their treatment partners was lacking. Stimulated by new payment structures ("integrale bekostiging van ketenzorg") in The Netherlands, a good incentive to join forces is offered.

In addition, the link between primary care and secondary care should be strengthened. Especially regarding establishment of correct respiratory diagnosis, collaboration between GPs and pulmonologists might be very beneficial. In Groningen (The Netherlands), GPs and pulmonologists have successfully been working closely together for many years regarding agreements and exchange of data.<sup>18</sup> Regarding diagnosis and treatment, it should be emphasized that there are several phenotypes of COPD, stressing the need for more targeted and tailored treatment within such collaborations.



Figure 2: Multidisciplinary care around the COPD patient

### *Integrating adherence measures and health status*

Developments in inhalation technology may be considered promising. However, solely focusing on adherence may not be sufficient. As previously highlighted, the ultimate goals of COPD treatment are prevention of exacerbations and maximizing quality of life.<sup>19</sup> As such, adherence is only an intermediate outcome. The MeMO-COPD study already indicated the potential value of combining non-adherence measures with health status when targeting high-risk COPD patients for interventions.

Health status measurement has gained increased attention in the past decade. To capture the full range of COPD patients' quality of life, several validated COPD-specific health status tools have been developed. Two of the most frequently used health status tools are the COPD Assessment Test (CAT) and the Clinical COPD Questionnaire (CCQ).<sup>20,21</sup> In current clinical practice, these tools are still under-used, most often evaluated only during regular patient consultations. Also, interventions following from these health status scores are generally reactive. In contrast, continuous digital monitoring of health status would enable more regular use of health status tools, early detection of worsening health status and symptoms and proactive interventions. Combined use of innovative inhalation technology and digital health status measures offer the potential to enhance adherence and tailor COPD management, potentially resulting in improved quality of life and reduced healthcare utilization and costs. A global outline of this approach is visualized in figure 3. It includes the use of a smart inhaler combined with a mobile phone application to measure adherence and health status, automatically generated tailored



decision support and motivational feedback, and optional digital or direct face-to-face contacts with healthcare providers or peer-patients. As depicted, several opportunities for tailored COPD management are offered (enhanced self-management and/or intensified guidance by health-care providers).

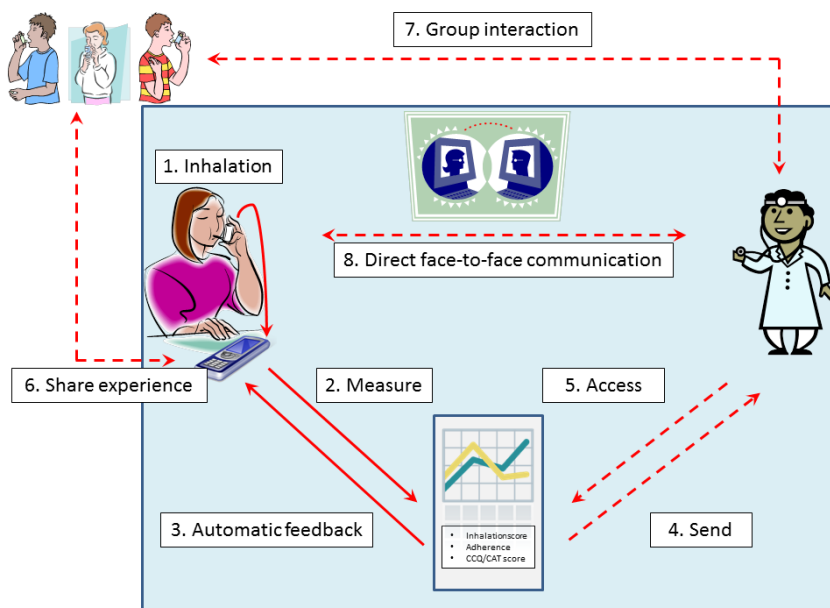


Figure 3: Integrated COPD management approach. Solid red lines: standard mHealth decision support; Dashed red lines: optional pathway, depending on patient preferences and feasibility studies

### *Tailoring the choice of inhalers, regimen and timing of intake to patients' preferences*

In addition to adapting treatment to patients' clinical phenotypes, tailoring treatment to patients' preferences and behaviour may be of equal importance, especially with the wealth of new inhaled treatments available. In RCTs, newest treatments have shown limited improvements in clinical efficacy, but considerable differences in dosing regimen and inhaler type exists, potentially impacting effectiveness in daily clinical practice. Most of the new pharmacotherapeutic options have a once-daily regimen which is, at first sight, likely to favour adherence. In other chronic diseases, once-daily regimens are associated with improved adherence<sup>22</sup>, whereas definitive evidence on the benefits of a once-daily regimen in COPD is yet lacking. COPD is a disease with fluctuating symptoms and different phenotypes and patients' individual preferences may play a major role. Price *et al* interviewed 2,138 COPD patients and it appeared that about 45% of them preferred a once-daily regimen, 30% a twice-daily and 25% had no preference.<sup>23</sup> A high self-perceived need for controller medication was associated with preference for a once-daily regimen. The choice of the drug regimen is related to the type of the inhaler,

and also patients' preferences regarding easiness of use of inhalers may differ.<sup>24</sup> Therefore, involving the patient in the choice of the inhaler and the dosing regimen should be considered. In addition, special attention should be paid to advising patients on the optimal time of medication intake. A recent survey indicated that the majority of patients suffering from morning symptoms were not taken their medication on time.<sup>25</sup> When concomitant use of multiple inhaled medications is indicated, the same inhaler is preferred as multiple-inhalers can confuse patients, resulting in worse outcomes.<sup>26,27</sup>

## Conclusion

Medication non-adherence in patients with COPD is associated with worse clinical and economic outcomes. Hence, interventions targeted towards non-adherent patients, such as MeMO and PHARMACOP, have shown to be a cost-effective strategy. Intervention costs and medication costs did slightly increase, however these costs were offset by gains due to prevention of hospitalizations. Therefore, improving adherence should be considered before adding new therapies. Moreover, large scale implementation and reimbursement of adherence enhancing interventions is recommended. Adherence-enhancing interventions should preferably use a multidisciplinary and targeted approach.

In addition, several potential targets for adherence enhancing interventions were identified, ranging from a specific population, the choice of inhaler device, a suitable period for inhalation technique training and the impact of reimbursement.

In particular, the COPD population of working-age was shown to be a potentially highly cost-effective population to target adherence-enhancing interventions on. In this population, interventions could not only affect direct healthcare costs, but also considerable impact on indirect costs, such as work productivity, can be expected.

The type of inhaler that is used by the COPD patient did not seem to affect treatment persistence. However, in order to avoid side-effects and improve medication effectiveness, the quality of COPD patients' inhalation technique should be closely monitored. It was found that side-effects are most prevalent in the first three months after inhaled corticosteroids initiation, implicating that in this time period inhalation technique interventions will have their greatest potential benefit.

Above all, smoking cessation remains of utmost importance in COPD patients that smoke. Reimbursement of pharmacologic smoking cessation treatment was shown to favour medication adherence, thereby strengthening the decision of the Dutch government to reimburse smoking cessation treatments.

To further optimize non-adherence management in patients with COPD, more research is needed regarding the particular effective contents of adherence-enhancing interventions, methods of monitoring adherence and consensus on the exact definition of non-adherence.

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